Selective Bromination of Aromatic Amines by Use of Tetrabutylammonium Tribromide and Benzyltrimethylammonium Tribromide

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Abstract

The reaction of aromatic amines with calculated amounts of tetrabutylammonium tribromide or benzyltrimethylammonium tribromide in dichloromethane-methanol containing calcium carbonate powder at room temperature gave, selectively, the objective mono-, di-, or tribromo-substituted aromatic amines in good yields.

In general, the reaction of aromatic amines (**1**) with bromine give polybromo-substituted derivatives or oxidation products because the aromatic amines have high reactivity.

Thus, it is difficult to carry out a step-by-step bromination of **1** with molecular bromine. For the purpose of the syntheses of monobromo-substituted aromatic amines from **1**, a technique in which the amino group convert to acetylamino group has frequently been employed.[1]

For the direct bromination of **1**, some brominating agents such as iodine monobromide[2], 2,4,4,6-tetrabromocyclohexa-2,5-dienone [3], hydrobromic acid-dimethylsulfoxide[4], N-bromosuccinimide-dimethylformamide[5], and hexabromocyclopentadiene[6] can be used instead of bromine.

Previous work in this series has shown that the reaction of **1** with benzyltrimethylammonium tribromide (BTMA Br_3)[7] 〈73b〉 and with benzyltrimethylammonium chlorobromate (BTMA Br_2Cl)[8] in dichloromethane-methanol at room temperature readily gave bromo-substituted aromatic amines(**2**), respectively. In this paper, we wish to report a selective bromination of **1** by use of tetrabutylammonium tribromide (TBA Br_3) (**3a**) and **3b**.

Results and Disccussion

The reaction of **1** with calculated amounts of **3a** or **3b** in dichloromethane-methanol containing calcium carbonate powder at room temperature gave the desirable mono-, di-, or tribromo aromatic amines in good yields. For instance, the reaction of aniline (**1a**) with 1.0 equiv of **3a** gave 4-bromoaniline (**2a-1**), and with 2.0 equiv of **3a** gave 2,4-dibromoaniline (**2a-2**); furthermore, the reaction with 3.0 equiv of **3b** gave 2,4,6-

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tribromoaniline in good yields, respectively.

Thus, selective bromination of **1** can be accomplished by using **3a** or **3b** properly.

Especially, we emphasize that the procedure using **3a** is a highly useful method for synthesizing monobromo-substituted aromatic amines. The results are summarized in the Table 1 (The results for an exhaustive bromination of several **1** with sufficient amounts of **3b** were already shown by us [7,8]).

The monobromination of less reactive **1**, such as 2-nitroaniline (**1x**), 3-nitroaniline (**1y**) and 4-nitroaniline (**1z**), were successfully carried out with **3b**.

We noticed that the presence of methanol markedly facilitated the bromination of **1**. In this case, the main active apecies is probably methyl hypobromite that may be produced from a reaction of TBA Br_3 or BTMA Br_3 with methanol. Reaction of **1** with methyl hypobromite would afford **2** and methanol. Methanol thus formed can be used repeatedly in the reaction cycle. Hydrogen bromide generated should be neutralized by added calcium carbonate. The reaction scheme leading to **2** by use of TBA Br_3 would be presented as follows;

$$(C_4H_9)_4N^+Br_3^- + CH_3OH \rightarrow (C_4H_9)_4N^+Br^- + CH_3OBr + HBr \quad (1)$$

$$\mathbf{1} + CH_3OBr \longrightarrow \mathbf{2} + CH_3OH \quad (2)$$

overall;

$$\mathbf{1} + (C_4H_9)_4N^+Br_3^- \longrightarrow \mathbf{2} + (C_4H_9)_4N^+Br^- + HBr. \quad (3)$$

Recently, Berthelot et al.[38] reported that **3a** is a useful paraselective monobrominating agent for some aromatic amines (**1a**, **1t**, **1a'**, N-cyclohexylaniline, and N,N-Dimethylaniline). We also confirmed the para-selectivity of the reaction by use of **3a** for **1**. However, as limitation of the procedure using **3a**, atemmpts at the monobromination of more reactive **1**, such as **1c**, **1e**, **1f**, **1h**, **1j**, **1l**, **1m**, **1p**, and **1r** were unsuccessful, and the mixtures of mono- and dibromo-substituted products of these compounds were obtained.

Experimental

4-Bromoaniline (2a-1) ; General procedure by use of 1.0 equiv of 3a: To a solution of aniline (**1a**) (0.50g, 5.37 mmol) in dichloromethane (30 ml)-methanol (20 ml) containing calcium carbonate (0.7g) was added dropwise **3a** (2.59g, 5.37 mmol) under stirring at room temperature. The mixture was stirred until a decoloration of the orange solution took place. The solid calcium carbonate was filtered off, the filtrate was concentrated, and to the obtained residue was added water (20 ml). The mixture was extracted with ether (40 ml x 4). The ether layer was then dried over magnesium sulfate and evaporated in vacuo to give a **2a-1** as colorless crystals; yeild 0.69g (75%) ; mp 62-63℃ (lit., [9] mp 63-64℃).

2,4-Dibromoaniline (2a-2) ; General procedure by use of 2.0 equiv of 3a: To a solution of **1a** (0.50g, 5.37 mmol) in dichloromethane (30 ml)-methanol (20 ml) containing calcium carbonate powder (1.5g) was added dropwise **3a** (5.18g, 10.74 mmol) under strring at room temperature. The mixture was stirred until a decoloration of the orange color solution took place. A subsequent same work-up as above gave **2a-2** as colorless crysals; yield 1.21g (90%) ; mp 79-81℃ (lit., [10] mp 79℃) .

2,4,6-Tribromoaniline (2a-3) ; General procedure by use of 3.0 equiv of 3b; To a solution of **1a** (0.50g, 5.37 mmol) in dichloromethane (50 ml)-methanol (20ml) was added **3b** (6.49g, 16.64 mmol) and calcium carbonate(2g) at room temperature. The mixture was stirred for 30 min until a fading of the orange color took place. A subsequent same work-up as above gave **2a-3** as colorless crystals; yield 1.65g (93%) ; mp 121-123℃ (lit., [11] mp 119-120℃)

2-Bromo-4-nitroaniline (2z-1) ; General procedure for the bromination of nitroaniline derivatives: To a solution of 4-nitroaniline (**1z**) (0.50g, 3.62 mmol) in dichloromethane (30 ml)-methanol (20 ml) containing calcium carbonate powder (0.7g) was added dropwise **3b** (1.41g, 3.62 mmol) under stirring at room temperature. A subsequent same work-up as above gave **2z-1** as yellow crystals; yield 0.74g (94%) ; mp 105℃ (lit., [34] mp 104.5℃) .

2-Bromo-4-ethylaniline (2g-1) : mp 23℃ (from methanol-water (1:3)). HNMR ($CDCl_3$) δ = 1.08 (3H, t, J=8Hz, CH_3), 2.42 (2H, q, J=8Hz, CH_2), 3.92 (2H, br.s, NH_2), and 6.38-7.42 (3H, m, Harom). Found: C, 47.89; H, 5.44;N, 7.15%. Calcd for $C_8H_{10}NBr$: C, 48.03; H, 5.64; N, 7.00%.

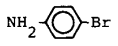
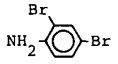
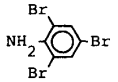
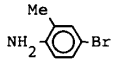
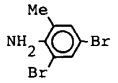
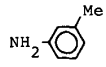
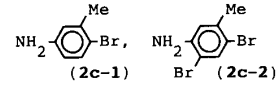
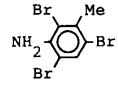
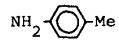
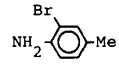
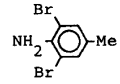
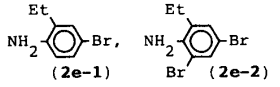
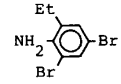
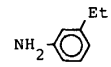
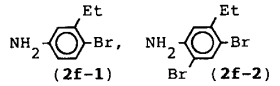
2,4-dibromo-5-methoxyaniline (2o-2) : mp 79-81℃ (from methanol-water (1:3)). δ = 3.77 (3H, s, OCH_3), 4.07 (2H, br.s, NH_2), 6.25 (1H, s, 6-H), and 7.43 (1H, s, 3-H). Found: C, 30.03; H, 2.43; N, 5.01%. Calcd for $C_7H_7NOBr_2$: C, 29.93; H, 2.51; N, 4.99%.

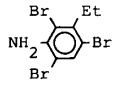
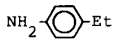
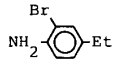
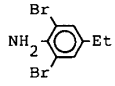
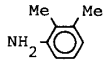
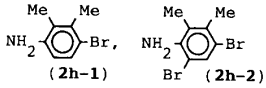
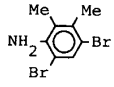
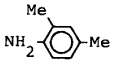
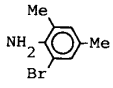
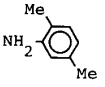
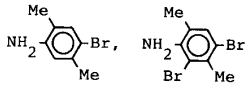
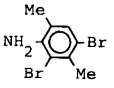
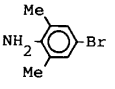
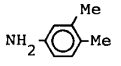
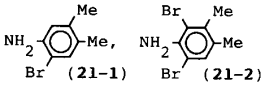
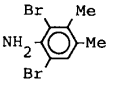
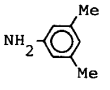
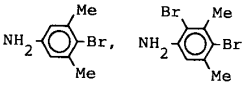
4-Bromo-2-ethoxyaniline (2q-1) : mp 38-40℃ (from methanol-water (1:3)) . δ = 1.27 (3H, t, J=7Hz, CH_3), 3.55 (2H, br.s, NH_2), 3.87 (2H, q, J=7Hz, CH_2), and 6.4-7.0 (3H, m, Harom). Found: C, 44.37; H, 4.61; N, 6.50%. Calcd for $C_8H_{10}NOBr$: C, 44.47; H, 4.66; N, 6.48%.

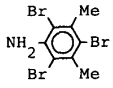
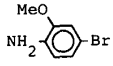
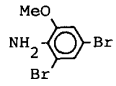
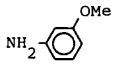
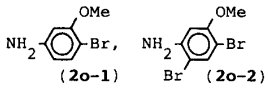
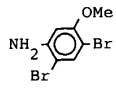
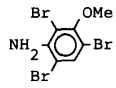
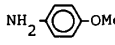
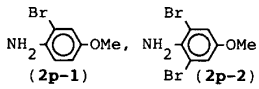
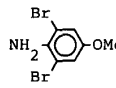
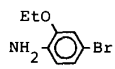
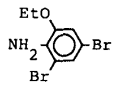
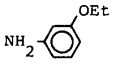
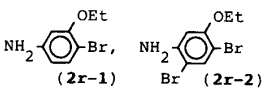
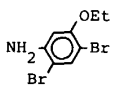
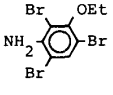
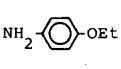
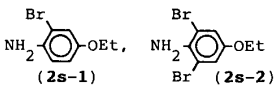
2,4-Dibromo-5-ethoxyaniline (2r-2) : mp 89℃ (from methanol-water (1:3)). δ = 1.37 (3H, t, J=7Hz, CH_3), 3.85 ((2H, q, J=7Hz, CH_2), 4.12 (2H, br.s, NH_2), 6.20 (1H, s, 6-H), and 7.45 (1H, s, 3-H). Found: C, 32.49; H, 3.02; N, 4.65%. Calcd for $C_8H_9NOBr_2$: C, 32.58; H, 3.07; N, 4.75%.

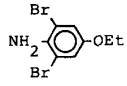
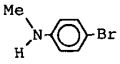
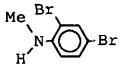
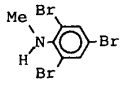
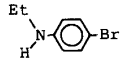
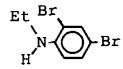
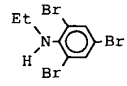
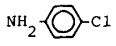
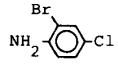
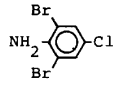
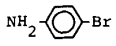
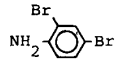
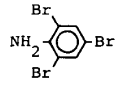
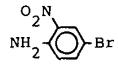
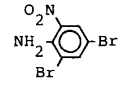
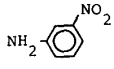
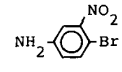
We wish to thank Dr. Mamoru Nakai and Mr. Katsumasa Harada, Ube Laboratory, Ube Industries, Ltd., for elemental analysis.

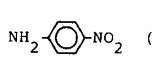
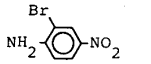
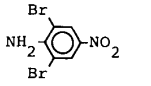
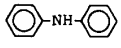
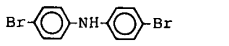
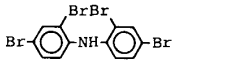
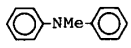
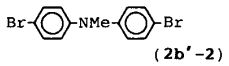
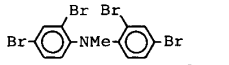
Table 1. Selective Bromination of Aromatic Amines by Use of TBA Br_3 and BTMA Br_3 at Room Temperature

Run	Substrate (1)	Reagent(3)[a] used	Molar ratio 3/1	Product (2)	Yield[b] (%)	Mp(°C) found	Mp(°C) reported
1	 (1a)	3a	1.0	 (2a-1)	75	62-63	66[9]
2		3a	2.0	 (2a-2)	90	79-81	79-80[10]
3[d]		3b	3.1	 (2a-3)	93	121-123	119-120[11]
4	 (1b)	3a	1.0	 (2b-1)	84	57-59	58-59[12]
5[d]		3b	2.1	 (2b-2)	94	44-45	46-47[13]
6	 (1c)	3a	1.0	 (2c-1) (2c-2)	-		
7		3a	2.0	(2c-1), (2c-2)	-		
8[d]		3b	3.1	 (2c-3)	91	101-102	101-101.6[14]
9	 (1d)	3a	1.1	 (2d-1)	82	oil	16-18[1]
10[d]		3b	2.1	 (2d-2)	94	75-76	79[15]
11	 (1e)	3a	1.0	 (2e-1) (2e-2)	-		
12[d]		3b	2.1	 (2e-2)	92	18-20	-[7]
13	 (1f)	3a	1.0	 (2f-1) (2f-2)	-		

14			**3a**	2.0	(**2f-1**), (**2f-2**)	-		
15[d)]			**3b**	3.1	 (**2f-3**)	94	68-70	-[7)]
16		(**1g**)	**3a**	1.0	 (**2g-1**)	87	23	-
17[d)]			**3b**	2.1	 (**2g-2**)	95	80-82	85[16)]
18		(**1h**)	**3a**	1.0	 (**2h-1**) (**2h-2**)	-		
19[d)]			**3b**	2.1	 (**2h-2**)	93	56-57	56[17)]
20[d)]		(**1i**)	**3b**	1.1	 (**2i-1**)	91	46-47	47-48[18)]
21		(**1j**)	**3a**	1.0	 (**2j-1**) (**2j-2**)	-		
22[d)]			**3b**	2.1	 (**2j-2**)	92	64.5-66	65[19)]
23[d)]		(**1k**)	**3b**	1.1	 (**2k-1**)	83	47-48	49-50[20)]
24		(**1l**)	**3a**	1.0	 (**2l-1**) (**2l-2**)	-		
25[d)]			**3b**	2.1	 (**2l-2**)	95	58-59	63[17)]
26		(**1m**)	**3a**	1.0	 (**2m-1**) (**2m-2**)	-		
27			**3a**	2.0	(**2m-1**), (**2m-2**)	-		

28[d]		**3b**	3.1	 (**2m-3**)	91	196-197	195[17]
29	 (**1n**)	**3a**	1.0	 (**2n-1**)	34[c]	60	60-61[21]
30[d]		**3b**	2.1	 (**2n-2**)	68[c]	25-26	27[22]
31	 (**1o**)	**3a**	1.0	 (**2o-1**) (**2o-2**)	-		
32		**3a**	2.0	 (**2o-2**)	92	79-81	-
33[d]		**3b**	3.1	 (**2o-3**)	95	83-84	-[7]
34	 (**1p**)	**3a**	1.0	 (**2p-1**) (**2p-2**)	-		
35[d]		**3b**	2.1	 (**2p-2**)	78[c]	79-80	81[23]
36	 (**1q**)	**3a**	1.0	 (**2q-1**)	70[c]	38-40	-
37[d]		**3b**	2.1	 (**2q-2**)	71[c]	53.5-54.5	52.5[24]
38	 (**1r**)	**3a**	1.0	 (**2r-1**) (**2r-2**)	-		
39		**3a**	2.0	 (**2r-2**)	88	89	-
40[d]		**3b**	3.1	 (**2r-3**)	93	93-94	-[7]
41	 (**1s**)	**3a**	1.0	 (**2s-1**) (**2s-2**)	-		

42[d]			**3b**	2.1		**(2s-2)**	78[c]	72-73	79[25]
43		**(1t)**	**3a**	1.0		**(2t-1)**	98	56-57	55[26]
44			**3a**	2.0		**(2t-2)**	99	46-48	48-49[27]
45[d]			**3b**	3.1		**(2t-3)**	93	37-39	39[27]
46		**(1u)**	**3a**	1.0		**(2u-1)**	86	oil	12[28]
47			**3a**	2.0		**(2u-2)**	88	82-83	85[28]
48			**3b**	3.1		**(2u-3)**	94	34-35	45[28]
49		**(1v)**	**3a**	1.0		**(2v-1)**	90	64-66	69[29]
50[d]			**3b**	2.1		**(2v-2)**	95	93-94	94[30]
51		**(1w)**	**3a**	1.0		**(2a-2)**	96	76-78	79-80[10]
52[d]			**3b**	2.1		**(2a-3)**	91	121-123	119-120[11]
53		**(1x)**	**3b**	1.0		**(2x-1)**	91	111	111.5[31]
54			**3b**	2.1		**(2x-2)**	76[c]	128-129	127[32]
55		**(1y)**	**3b**	1.0		**(2y-1)**	72[c]	131	131-132[33]

56	 (1z)	3b	1.0	 (2z-1)	94	105	104.5[34]
57		3b	2.1	 (2z-2)	97	207	206-207[35]
58	 (1a')	3a	2.0	 (2a'-2)	93	106-107	105.5-106[36]
59[d]		3b	4.1	 (2a'-4)	90	189-190	182[37]
60	 (1b')	3a	2.0	 (2b'-2)	99	118-119	119[37]
61[d]		3b	4.1	 (2b'-4)	95	142	142[37]

a) **3a**: Tetrabutylammonium tribromide (TBA Br_3).
3b: Benzyltrimethylammonium tribromide (BTMA Br_3).

b) Yield of isolated product.

c) Product was isolated by column chromatography on alumina.

d) This run was already reported by us in our paper[7].

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